REMARKS

Claims 1-16 are pending. Claims 3, 6, and 7 stand cancelled. Claims 1, 2, 9, and 16 are currently amended. Claim 17 has been added. Applicants submit that no new matter has been added as a result of this amendment; support therefor can be found throughout the specification and original claims. For example, support for amended claim 1 can be found in paragraph 1 of the specification, and support for new claim 17 can be found in paragraph 0056.

As an initial matter, it is believed the amendments may be properly entered at this time, i.e. after final rejection, pursuant to 37 CFR §1.116, because the amendments do not require a new search or raise any new issues, and they reduce issues for appeal. Indeed, it is respectfully submitted that the within amendments place the application in condition for allowance. Thus, entry of the amendments at this time is earnestly solicited.

As a further initial matter, Applicant thanks the Examiner for his time and courtesy during the informal telephonic interview on July 14, 2008. No agreements were reached.

Claim Objections

The Examiner has objected to claims 5, 9, and 16.

The Examiner asserts at page 3 of the Office Action that the term "Kozak sequence", recited in claim 9, must be referred to by its sequence identification number to comply with 37 CFR 1.821. The instant specification states at page 4, paragraph 0081 of US 2004/0268432 that "Kozak sequence, which is a sequence for effectively translating mRNA in eukaryote (Kozak, 1989) is attached prior to the initiation codon." The Kozak et al. reference cited in the instant specification presents the consensus Kozak sequence. Further, the Kozak sequence is included as part of the sequence of the designed refre1 nucleic acid presented in Figure 9 and SEQ ID NO: 1 of the instant application.

Applicant submits that the Kozak sequence (ACCATGG) is well known in the art. In fact, this sequence is readily identified in a Google Search by searching for "Kozak sequence." However, to overcome the objection and without altering the scope of the claim, the Applicant has inserted the nucleic acid sequence for a Kozak sequence into the claim.

The Examiner asserts on page 4 of the Office Action that an improper article is present before "GT" in line 4 and suggests the insertion of –the—rather than "a". The article before "GT" in claim 5 is "the". Withdrawal of the objection is respectfully requested.

The Examiner asserts on page 4 of the Office Action that claim 16 is improper for containing an informality for not including the language "wherein said seed comprises the heterologous nucleic acid." The language has been added to the end of claim 16 for the purpose of formality. The scope of the claim is not changed.

In view of all of the above, Applicants respectfully request reconsideration and withdrawal of the objections.

Claim Rejections

Rejection of Claim 2 under 35 U.S.C. §112, second paragraph

Claim 2 is rejected under 35 U.S.C. §112, 2nd paragraph, for alleged indefiniteness. Without acquiescing to the grounds for rejection, Applicant has amended claim 2 to delete the allegedly indefinite term "derived" from the claim. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-2, 4-5, and 8-16 under 35 U.S.C. §112, first paragraph

Enablement

The Examiner has rejected claims 1-2, 4-5, and 8-16 under 35 U.S.C. §112, 1st paragraph. The Office Action alleges that the specification, "while being enabling for modified yeast FRE1 coding sequence as defined in SEQ ID NO: 1…does not

reasonably provide enablement for the scope of possible gene sequences from any species claimed for use in plants." (Office Action, p.5). Applicant respectfully traverses the rejection.

The claims were previously amended to recite specific polyadenylation signal sequences. Amended claim 1 recites "wherein the polyadenylation signal sequence is selected from the group consisting of ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA and AATAAN of which N is A, G, C or T." The claims have also been amended to recite "the GT rich sequence is 8 or more consecutive G and/or T nucleotides." The Office Action alleges that "the specification as filed does not provide any other example genes which would require such modification other than the yeast FRE1 gene for expression in tobacco" (page 6).

During the telephonic interview with the Examiner, it was agreed that one of skill in the art could readily "recognize" the specific sequences listed in the claims, by manual or automated searching, but the Examiner alleged that one would not necessarily be able to determine which sequences would constitute polyadenylation sequences in plants. It was also agreed that those of skill in the art do not carry in their minds nucleic acid sequences for genes that can be "instantly recalled," but that instead those of skill in the art used databases such as BLAST or other amino acid and nucleotide sequence databases to "instantly recall" such sequences.

Applicant submits that the specification provides other genes that may require modification of the coding sequence using the methods of the invention, and cites references that demonstrate that it was well known in the art that expression of heterologous genes in plants was often difficult, and that heterologous proteins were expressed at low levels. For example, the specification states:

> [0014] Example of such incomplete transcription, in which gene of another species is transformed into the higher plant, is gene group Cry encoding .delta.-endotoxin (insecticidal protein) of Bacillus thuringiensis. More than 42 Cry genes have been known and are classified into 4 classes (cryI-cryIV)(Whiteley and Schnepf, 1986). The gene encoding this

insecticidal protein was introduced into the higher plant, but neither expression nor extremely low expression was found.

[0015] This may be caused by (1) difference in codon usage, (2) high AT content in Cry gene, (3) unstable in mRNA, and (4) a partial splicing of Cry gene as intron.

[0016] A preparation of the transgenic plant with high expression of protein has been reported. Namely, in order to express Cry gene group efficiently in the higher plant, base sequence of Cry gene is modified to arrange with base sequence of the plant, and the primer is synthesized, then is completely synthesized by PCR (Perlak et al., 1991, Fujimoto et al., 1993, and Nayak et al., 1997). (bridging pages 3-4)

A number of members of the large family of Cry genes are useful for expression in plants for their insecticidal activity. Problems with exploiting such proteins for their insecticidal activity due to low expression of these genes in plants was well known at the time of filing of the instant application. Moreover, those of skill in the art were well able to identify proteins with low expression, and frequently able to determine the reasons for the low expression (e.g., truncated transcript, premature polyadenylation, codon usage, etc.) This is demonstrated by a number of references cited in the specification and in the IDS, for example Fujimoto (1993) and Perlak (1991) which are both cited in the specification, and Van Der Salm, Diehn, and Iannacone, which are cited in the IDS and were known in the art prior to the date of filing of the instant application. In addition to the Cry genes, the specification also notes a number of genes involved in iron absorption that may also be useful for plants.

Applicant submits that one of skill in the art could "instantly recall" the sequences of the Cry genes using the NCBI nucleotide database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=nuccore&itool=toolbar) as demonstrated by the attached search results. Moreover, one of skill in the art could recognize the putative polyadenylation signal sequences (noted with a single underline) and the GT rich regions (noted by the double underline) in the example Cry sequence provided (also attached).

The Office Action alleges that "other than a vague teaching to look for GT-rich areas in any such gene, and change the sequence to remove certain sequences, one of skill in the art would not immediately envision on what is otherwise any possible heterologous nucleic acid gene sequence as broadly claimed" (at page 6). Applicant submits that the definition of a GT rich region as "8 or more consecutive G and/or T nucleotides" is in no way vague and that such sequences can be easily identified by scanning the nucleotide sequence. Applicant submits that the terms "8 or more", "consecutive", and "G and/or T" are definite and that a list including all of the possible sequences of 8 nucleotides in length falling within the scope of the definition could be readily generated by one of skill in the art with no further guidance than provided by the claim.

Moreover, the claims are directed to a method for modifying a heterologous nucleic acid sequence that contains a polyadenylation signal sequence of ATs and a GT rich region, not a sequence. Applicants are NOT required to explicitly describe each and every known or yet to be discovered heterologous nucleic acid sequence that may be of used in the claimed methods. In fact, the practice of providing each and every sequence is discouraged by both the Patent Office and the court, "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification" (*Falkner v. Inglis,* No. 05-1324, US Court of Appeals for the Federal Circuit, May 26, 2006). Having provided a series of examples of sequences that might be modified by the methods of the invention demonstrates that the Applicant was in possession of the invention at the time of filing.

The Office Action cites Grec to demonstrate the allegedly cryptic nature of polyadenylation sequences in PDR5 and MIP genes. The references is not relevant to the instant claims as the sequences could not be modified by the methods of the instant claims as they do not include the required sequences for modification. Moreover, the Examiner's statement that "no AATAAA related elements were found upstream of the cryptic poly A sites of PDR5 or MIP genes" demonstrates that one of skill in the art can readily identify the sequences, or the lack thereof, recited in the claims.

The gist of the present invention is to avoid an addition of undesired polyadenylation onto mRNAs by modifying one or more polyadenylation signal

sequence of ATs and GT rich regions, by which the heterologous nucleic acid is expressed in the transformed useful plant with high efficiency (refer to page 5, last 4 lines).

The addition of polyadenylation onto mRNA is determined by the presence of polyadenylation signals which is irrespective of a function of polypeptide encoded in the mRNA. The function of FRE1 itself is not involved in the addition of polyadenylation in Example of the present invention because the amino acid sequence of FRE1 is not altered by the modification of the polyadenylation signal of ATs and GT rich regions.

Further, the present application explicitly demonstrates that the presence of polyadenylation signal of ATs and GT rich regions in the heterologous nucleic acid causes undesired polyadenylation by which the expression of mature mRNA of the heterologous nucleic acid is suppressed, which evidently means that polyadenylation signal of ATs and GT rich regions are polyadenylation signals in plant. In addition, the present application explicitly demonstrate that the modification of polyadenylation signal of ATs and GT rich regions enhances the expression level of the heterologous nucleic acid irrespectively of a function of polypeptide encoded therein.

Considering the fact that the addition of polyadenylation onto mRNA is determined by the presence of polyadenylation signals, not on the function of the gene, the inclusion of a long list of genes that can be used in the method of the invention is not required. It is apparent from the disclosure of the instant application that the enhancement of the expression level of any heterologous nucleic acid would be observed by the claimed invention only if the heterologous nucleic acid comprises the polyadenylation signals of ATs and GT rich regions.

Grec et al. teaches that there are various polyadenylation signals in plant. Grec et al. never teaches, however, that the polyadenylation signals of ATs and GT rich regions in the heterologous nucleic acid cannot be a polyadenylation signal in plant. On the other hand, the present invention is to avoid an addition of undesired polyadenylation onto mRNAs caused by the presence of polyadenylation signal of ATs and GT rich regions. This claimed invention is fully supported by the instant specification. The present invention is not related to a method for inhibiting <u>any</u>

polyadenylation caused by any polyadenylation signals. The teaching of Grec et al. that there are various polyadenylation signals in plant such as PDR5 or MIP is therefore irrelevant to the present invention because heterologous nucleic acids such as PDR5 and MIP are not the heterologous nucleic acid of the present invention which include polyadenylation signals of ATs and GT rich regions.

Likewise, the fact that 3' processing of transcripts in plant was very complex and not well understood at the time of filing of the instant application is irrelevant to the present invention. It is amply demonstrated in the specification that the presence of polyadenylation signals of ATs and GT rich regions is a polyadenylation signal even if the mechanism of the addition of polyadenylation caused by them is not clear.

Further, the identification of AT sequence motifs and GT rich regions in the heterologous nucleic acid and the modification thereof without inactivating the protein encoded in the heterologous nucleic acid is well within the ability of the skilled person. With reference to "without inactivating the protein encoded in the heterologous nucleic acid", it is specifically disclosed in the specification as filed (e.g., see first paragraph of the specification). For example, the polyadenylation signals of ATs and GT rich regions are modified but the amino acid sequence encoded at such signals are not altered. Moreover, the use of the degeneracy of the nucleotide coding sequence to include silent mutations is well known in the art and is discussed in any college, if not high school biology text book. For example, Perlak teaches the modification of coding sequences such that 9.5% or 60% of the codons are different from those in the original nucleic acid sequence, without changing the amino acid sequence encoded by the nucleic acid. Applicant notes that Perlak was published 8 years prior to the filing of the instant application, demonstrating that codon substitution is well within the ability of those of skill in the art.

The Office Action cites *Genetech, Inc. v. Novo Nordisk, A/S* (citation omitted) to demonstrate that specification provides insufficient guidance as to what modifications can be made to a sequence to modify the polyadenylation signals of ATs and GT rich regions as claimed. Applicant submits the facts in *Genetech v. Novo Nordisk* were substantially different from those in the instant case. The claims in the case were drawn to a method that had been attempted by many, expression of functional human

proteins as fusion proteins with protease specific cleavage sites, and subsequent cleavage of the protein to produce a specific product. Specifically, the Court stated:

> The limited testimony regarding the knowledge of one skilled in the art offered by Genentech at the preliminary injunction hearing, and relied upon by the district court, is further undermined by the fact that no one had been able to produce any human protein via cleavable fusion expression as of the application date. If, as Genentech argues, one skilled in the art, armed only with what the patent specification discloses (a DNA sequence encoding a human protein, in this case, hGH, and a single example of an enzyme and its cleavage site), could have used cleavable fusion expression to make a human protein without undue experimentation, it is remarkable that this method was not used to make any human protein for nearly a year, see Shine et al. , 285 *Nature* 456 (June 1980), or to make hGH for five years. See *Belagaje et al.* , 3 *DNA* 120 (1984). Certainly, DNAs encoding desirable human proteins were known at the time of filing (e.g. , insulin, described in the British patent), and a great many researchers were attempting to produce human proteins using recombinant DNA technology. This failure of skilled scientists, who were supplied with the teachings that Genentech asserts were sufficient and who were clearly motivated to produce human proteins, indicates that producing hGH via cleavable fusion expression was not then within the skill of the art.

An essential aspect of the instant invention is not generally the method of inserting mutations that do not substantially alter protein function or the sequence of the encoded protein, instead the invention relies on mutation of the coding sequence at specific sites, particularly putative polyadenylation signals of ATs and GT rich regions. Making such mutations in coding sequences is well within the ability of those in the art as demonstrated by Perlak. References cited in the Office Action, for example Keskin and Guo demonstrate that the generation of modified proteins and their testing for function is routine and well within the ability of those of skill in the art.

In re Wands states:

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (pg. 1404, emphasis added)

Applicant submits that there is no prohibition against routine empirical testing within the scope of enablement. During prosecution Wands submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas. The need to repeat experiments was deemed to be routine.

Of all of the fusion experiments performed by Wands, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. This level of success was deemed to be sufficient to meet the requirement of enablement. Enablement does not require that every experiment work the first time. Experimentation, by its nature, has at least some aspect of uncertainty which is allowed. Wands did not teach an improved method for making hybridomas. Wands taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies that fall within the limitations of the claims is unknown.

The instant claims are directed to a method to modify a nucleic acid sequence identified as including specific nucleic acid sequences to disrupt the specific sequences without disrupting the function of the protein. Such methods of mutation and testing are well within the ability of those of skill in the art. Although some experimentation may be necessary to practice the claimed methods, the experimentation is routine and well within the ability of those of skill in the art.

Applicant accordingly requests that the rejection be reconsidered and withdrawn.

Written Description

The Examiner has rejected claims 1-2, 4-5, and 8-16 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner argues that "the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art

that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action, p. 8). Applicant respectfully traverses the rejection.

The claims were previously amended as set forth above to recite the specific sequences, present in some nucleic acids, to be modified. As discussed during the telephonic interview and as noted above, it was agreed that those of skill in the art would be able to identify the claimed AT and GT sequences within nucleic acid sequences. If Applicant is incorrect in this understanding, Applicant requests that the Examiner make clear what is unclear regarding the number "8" or the terms "consecutive" or "G and/orT", and why a "recognized definition" of the phrase would be required. Also, as discussed above, the specification provides a number of genes for use in the method of the invention. Those of skill in the art are rarely in possession of complete nucleotide sequences in their minds, but instead are in possession of knowledge on nucleic acid and amino acid sequence databases and their use. One of skill in the art would understand that the inventors were in possession of such knowledge.

Applicant respectfully submit the written description requirement does not necessitate an encyclopedic recounting of all known and yet to be discovered sequences, including variants and alternate isoforms, that might be used in the claimed methods when a generic description is provided. To hold the Applicant's claimed methods to this kind of standard is inappropriate and deprives the Applicant of protection for the full scope of the claimed invention. Furthermore, Applicant has provided not just a generic description, but both working examples and a number of genes that could be modified using the methods of the invention. One of ordinary skill in the art, armed with the specification, would not only be able to practice the methods as currently claimed, but would also recognize Applicant to be in possession of the invention as instantly claimed at the time the application was filed.

Applicant's arguments are strongly supported by recent Federal Circuit decisions. For example, In *Union Oil Co. v. Atlantic Richfield Co.* 208 F.3d 989, 997 (Fed. Cir. 2000), the court concluded, "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." In accordance with this

conclusion, Applicant provides explicit examples of Cry genes or iron fixing genes that can be used in the methods of the invention.

Therefore, in view of the teachings of the instant specification, the claims clearly meet the written description requirement. Applicant respectfully requests reconsideration and withdrawal of the rejection.

New Matter

The Office Action has rejected claim 1 for containing new matter for the phrase "8 or more consecutive G and/or T nucleotides". Applicant points to paragraph 134 of the instant specification reproduced below:

> [0134] The present invention provides a method for designing base sequence for obtaining full length transcriptional product by transferring gene of different species in the higher plant. In the method of the present invention, in order to avoid addition of poly(A) in the coding region, it was found that it is necessary to design the sequence consisting of continued base sequence of 8 bases or more without containing sequence consisting of only G or T, and to design the sequence without containing not only a sequence of AATAAA but also a sequence, in which any one of bases thereof is replaced by another base (i.e. NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, or AATAAN). [emphasis added]

Per section 2163.02 of the MPEP, "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." Applicant submits that one of skill in the art would have understood the inventor to be in possession of the subject matter claimed at the time of filing. Withdrawal of the rejection is respectfully requested. However, if the Examiner will not withdraw the rejection, Applicant request that the Examiner provide language that may be acceptable and be considered to be supported by the specification.

Rejection of Claims 1, 4-5, 8, 14, 15, and 16 under 35 U.S.C. §103(a)

Claims 1, 4-5, 8, 14, 15, and 16 are rejected under 35 U.S.C. §103(a) over Perlak et al. in view of Joshi.

Applicant respectfully disagrees.

It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection are requested.

Perlak et al. teach that the modification of heterologous nucleic acids encoding Bacillus proteins increases the levels of these proteins. The modification is, however, the alteration of a potential polyadenylation signal sequences which is 4 or more consecutive A or T without altering the amino acid sequence as described at "Modifications of the Coding Sequence of Insect Control Genes" in pages 3324 and 3325, which increases the G+C content as a matter of course. In other words, Perlak et al. does not consider that GT rich sequence could be a polyadenylation signal in a combination of ATs.

Joshi at al. states that "certain domains of the 3' untranslated regions in forty-six nuclear genes of higher plants have been examined and search made for putative poly (A) signals" (lines 10-12, page 9629). Joshi also teaches that YGTGTTYY was found in the 50 bases downstream from AATAAA in Domain IV" (lines 3-24, page 9637). Applicant notes that the sequence taught by Joshi has only 5 consecutive G and/or T residues, not 8 as required in the instant claims. Moreover, Joshi requires a match of only 5 of 8 of the nucleotides which is clearly distinct from the instant claimed invention.

Applicant assumes that Y is a pyrimidine. Therefore, the sequence of Joshi could be CGTAAACC.

Thus, Joshi et al. is related to the naturally-occurring polyadenylation in the 3' processing of mRNA of the plant genes whereas no teaching or suggestion is found in Joshi at al. that the combination of a GT rich sequence and ATs in a heterologous nucleic acid could be a polyadenylation signal in plant. There is no teaching or suggestion that the removal of such sequences, required for expression of plant genes, and required for expression of mammalian genes, should be removed from heterologous sequences for expression in plants.

Actually, it is not obvious that the combination of GT rich sequence and ATs could be a polyadenylation signals at the time of the priority date of the instant application. As a support for this, we are pointing out the description of Diehn at al. which was a document BD listed in IDS filed on August 18, 2003.

Diehn et al. teaches that the premature polyadenylation can limit the expression of a foreign gene (BT toxin, for example) in plant wherein such polyadenylation is caused by the UG-rich sequences at the upper stream and AT rich sequences including AATAAT at the down stream of the gene (refer to Figure 6 in page 1440).

Diehn et al. states that "to the best of our knowledge, this study is the first to show that sequence with the coding region of a foreign gene can be recognized as polyadenylation signals by plant". Diehn et al. was published in August 1998 which is later than the priority date of the instant application (March 1998). Thus, "sequence with the coding region of a foreign gene can be recognized as polyadenylation signals by plant" would not have been obvious for the skilled person at the time of priority date of the instant invention; therefore, the gist of the present invention of the avoidance of an addition of undesired polyadenylation onto mRNAs by modifying the polyadenylation signal sequence ATs and GT sequences in a heterologous nucleic acid is not obvious either over Perlack et al. and Joshi et al.

Claim 9 is rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Perlak in view of Joshi further in view of Kozak. Applicant respectfully disagrees. For at least the reasons set forth above, the combination of Perlak and Joshi neither

teaches nor suggests the instantly claimed invention. Kozak does nothing to remedy this deficiency. Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance.

FEE AUTHORIZATION

The Commissioner is authorized to charge the fee for a one month extension in time for reply that is hereby requested to our Deposit Account, No. 04-1105, Reference 55022DIV(71526). Although it is not believed that any other fees are due, the Commissioner is authorized to charge any other fees associated with this submission to the Deposit Account noted. Any overpayment should be credited to said Deposit Account.

Dated: September 5. 2008

Respectfully submitted,

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